ATTEMPTED BLOCKING OF THE LSD REACTION WITH BAS

#94

These experiments were carried out because it is known that BAS is a powerful anti-serotonin and the possibility existed that the LSD psychosis was due to an accentuation of the effects of serotonin within the central nervous system (LSD in low concentration potentiates rather than blocks the effects of serotonin in smooth muscle preparations).

The subjects used were 10 of the same 15 Negro male, former drug addicts who served in the experiments dealing with the acute effects of BAS. These patients received the following drug combinations in a randomized order (Latin square): BAS placebo plus LSD placebo; BAS plus LSD placebo; BAS placebo plus LSD; and BAS plus LSD. Doses of BAS were 150 mg. every six hours for four doses (total dose 600 mg.). The last dose was given two hours before LSD. LSD was administered orally in doses ranging between 0.5-1.5 mcgm./kg. (average of 1.1 mcgm./kg.). The smaller doses were given to the men who were tested first since the possibility existed that BAS and LSD might synergize.

Encl. 2

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Methods. The methods used included determination of pupillary size, threshold for knee jerk, resting systolic blood pressure, response to a modification of the Abramson-Jarvik questionnaire, and evaluation of the clinical grade of the LSD reaction based on short psychiatric examinations. These methods and the means of statistical analysis employed have been previously described in other reports.

The results are shown in the accompanying table. The only important change noted was significant blocking of LSD induced elevation in blood pressure by the BAS. All other aspects of the reaction including mental response, were unaffected. A number of patients withdrew from all experiments after these tests were completed, primarily because of long persistence of the unpleasant BAS effects.

Discussion. The results do not favor the hypothesis that LSD psychosis is due to potentiation of serotonin effects within the central nervous system. They, however, do not exclude this possibility since we do not know whether the symptoms caused by BAS are due to peripheral or to central actions.

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ATTEMPTED BLOCKING OF LSD REACTION WITH BAS

EASURE	DRUG			
	BAS PLACEBO + LSD PLACEBO	BAS + LSD PLACEBO	BAS + LSD	BAS PLACEBO + LSD
...illar Reflex	+ 0.13 ± 0.14	+ 1.17 ± 0.17	+ 2.04 ± 0.29	+ 2.02 ± 0.43
...upillary Size	- 0.11 ± 0.22	+ 1.37 ± 0.55	+ 3.79 ± 0.35	+ 4.54 ± 0.28
...ystolic Blood Pressure	+ 0.59 ± 0.18	+ 0.12 ± 0.31	+ 0.76 ± 0.36	+ 2.48 ± 0.46
...mber of Questions	0.7 ± 0.9	5 ± 0.3	43 ± 12	42 ± 13
...linical Grade	0 ± 0	0.3 ± 0.3	1.1 ± 0.1	1.3 ± 0.1

Dose of LSD = 0.5 - 1.5 mcg./kg. (ave. 0.95 mcg./kg.)

Dosage of BAS = 600 mg. in 24 hours given in 4 doses of 150 mg.

Figures are means of observations on 10 subjects ± standard errors.

ACUTE EFFECTS OF LARGE DOSES OF BOL IN MAN

(95)

D-2-Brom-lysergic acid diethylamide (BOL) differs from LSD only in the presence of a bromine atom at carbon No. 2. This material is a potent anti-serotonin *in vitro*. Rothlin *et al* have reported that the doses of BOL 20 times greater than those of LSD do not induce a psychosis in man. Since, like LSD, BOL reverses prolongation of hexobarbital sleeping-time by serotonin it must be presumed that the drug does reach the central nervous system. These experiments have been interpreted as not favoring the hypothesis which attributes the LSD psychosis to inhibition of brain serotonin by LSD.

It occurred to us that, because of the chemical similarity of the two compounds BOL might possibly block the LSD reaction. It was first necessary to re-evaluate the acute effects of this substance in man.

Subjects used were 15 Negro male addicts who had been abstinent from opiates for at least three months. All of these subjects had had considerable experience with the subjective effects induced by LSD.

BOL was given orally. Initial doses were 5 mcgm./kg. of bodyweight, which was increased in step-wise fashion, as the experiments proceeded to almost 90 mcgm./kg. The highest total dose given was 8 mg.

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Observations. The following observations were made two hours before and for one hour after the administration of BOL: rectal temperature, resting pulse rate, respiratory rate, resting systolic and diastolic blood pressures, threshold for elicitation of kneejerk, pupillary size, modification of the Abramson-Jarvik questionnaire, and a short psychiatric examination.

Results. Doses of BOL up to 4 mg./70 kg. caused neither subjective nor objective effects. Doses of 4 mg. or more per 70 kg. of bodyweight induced mild effects, which are presented in the table. These included small increases in systolic blood pressure, diameter of the pupil, and in the threshold for kneejerks. The "mental" symptoms included nervousness, nausea, chilly sensations, blurred vision and, in some patients, colored lights and hallucinations. Reactions are described as resembling those of a very small dose of LSD and were milder than the effects of 0.5-1.5 mcgm. of LSD in the same subjects (see table). It is estimated that the effects are no greater in degree than those induced by 0.25-0.5 mcgm./kg. of LSD. BOL is, therefore, at least 100-200 times less potent than LSD. It is, in fact, far less potent than lysergic acid monoethylamide (LAE).

Discussion. These results confirm those of Rothlin and do not favor the hypothesis which attributes the LSD psychosis to a "deficiency" of serotonin.

EFFECTS OF 5-8 MG./70 KG. OF D-2-BROM-LYSERGIC ACID DIETHYLAMIDE

ASURE	DRUG		
	PLACEBO	BOL [1]	LSD [2]
tellar Reflex [3]	+ 0.15 ± 0.12	+ 0.68 ± 0.2	2.29 ± 0.32
pillary Size	- 0.16 ± 0.18	+ 1.54 ± 0.33	4.93 ± 0.36
stolic Blood Pressure	+ 0.68 ± 0.2	+ 0.95 ± 0.3	2.69 ± 0.3
mber of Questions	2 ± 1.2	13 ± 4.7	61 ± 11
inical Grade	0 ± 0	0.6 ± 0.15	2.0 ± 0.3

1 Average dose of BOL = 6.0 mg./70 kg. = 86 mcg./kg.

2 0.5 to 1.5 mcg. of LSD/kg. (Average = 1.1 mcg./kg.).

3 Figures are means on 15 subjects ± standard errors.